EXHIBIT C
REPLACEMENT PARAGRAPHS, MARKED

At page 20, line 27 to page 21, line 1 of the specification, the change is as marked:

FIG. [11] 7. Mouse *ltbp-2* cDNA Clones. The schematic figure presents overlapping mouse cDNA clones representing the mouse *ltbp-2* coding sequence. A partial representation of the restriction sites is shown. A, *Avr*II; N, *Nae*I; Sa, *Sca*II; X, *Xho*I; B, *Bam*HI; C, *Cla*I; and E, *Eco*RI.

At page 21, lines 3-22 of the specification, the changes are as marked:

FIG. [12A] 8A. *ltbp-2* Gene Expression in the Developing Mouse Skeleton. Shown is an overview of the of the *ltbp-2* gene during mouse development, as determine by tissue in situ hybridization. The figure presents an autoradiogram made by direct exposure of tissue sections to film after hybridization with radiolabeled probes, but before dipping slides in radiographic emulsion. Day 16.5 p.c. sections contain whole embryos sectioned in the mid-sagittal plane. Identical conditions were maintained throughout autoradiography and photography, making it possible to compare the overall strength of hybridization with antisense (top) and sense (bottom) probes. 1 cm = 20 mm.

FIG. [12B] 8B. *ltbp-2* Gene Expression in the Developing Mouse Skeleton. Shown is a selected brightfield microscopic view of mouse *ltbp-2* gene expression in cartilage of day 16.5 p.c. mouse embryos. Photograph was taken from tissue sections following a two week exposure to photographic emulsion. 1 cm = 20 mm.

FIG. [12C] 8C. *ltbp-2* Gene Expression in the Developing Mouse Skeleton. Shown is a selected darkfield microscopic view of mouse *ltbp-2* gene expression in cartilage of day 16.5 p.c. mouse embryos. Photograph was taken from tissue sections following a two week exposure to photographic emulsion. In all darkfield photographs red blood cell and other plasma membranes give a faint white signal that contributes to the background of the study. 1 cm = 20 mm.

At page 62, line 18 to page 63, line 5 of the specification, the changes are as marked:

In this study, the inventors isolated and characterized a novel murine fibrillin-like cDNA encoding LTBP-3. To clone the murine LTBP-3 gene, cDNA from a 3T3 cell cDNA library was amplified using human fibrillin-1 PCR™ primers under low stringency conditions (*i.e.*, annealing at 37°C initially for 10 cycles, followed by annealing at 60°C for 30 cycles). The results indicated that a murine DNA fragment of unexpectedly low homology (~50%) to human fibrillin-1 was obtained. Molecular cloning of the authentic murine fibrillin-1 transcript was also performed, confirming the human and murine fibrillin-1 coding sequences share >95% sequence identity.. The murine fibrillin-1 and PCR™ sequences were different, which suggested that the PCR™ product may have been derived from a related, fibrillin-like cDNA. The 3T3 cell cDNA library was screened at high stringency using the murine PCR™ product as the probe in order to test this hypothesis. A cDNA walking strategy eventually yielded seven overlapping cDNA clones (FIG. 1). It provides a unique mRNA of 4,314 nucleotides, with an open reading frame of 3,753 nucleotides (SEQ ID NO:3) [(FIG. 9)]. The deduced molecule is a unique polypeptide of 1,251 amino acids (SEQ ID NO:4) [(FIG. 10)]. Excluding the signal peptide (21 amino acids), the novel fibrillin-like molecule consists of five structurally distinct regions (Region 1-Region 5), and although similar to murine fibrillin-1 (FIG. 2A), its domain structure is unique as is evidenced by the schematic representation of LTBP-3 shown in FIG. 2B.

At page 75, lines 7-11 of the specification, the change is as marked:

In co-transfection studies of 293T Cells using pLTBP-3fl and pTGF-b1, immunoprecipitation of LTBP-3 and TGF-b1 was demonstrated by 293T cells following transient transfection and radiolabeling. Aliquots (~10^6 incorporated CPM) of radiolabeled media were immunoprecipitated and separated using 4%-18% gradient SDS-PAGE and either reducing or nonreducing conditions as described (Yin et al., 1995) [(FIG. 13)].

At page 75, line 21 to page 76, line 11 of the specification, the change is as marked:

To identify new murine LTBP family members, independently designed degenerate oligonucleotide primers were synthesized based on a structural homology shared by human LTBP-1 and mouse LTBP-3 coding sequences: forward primer, 5'-AAACGTCACACGTGAIACGTGAACGTTGCTTGCTGG-3' (SEQ ID NO:12); reverse

primer, 5'-TTACGTCCACGTACACGTCTAGCAAGCAAGCA-3' (SEQ ID NO:13), and then used PCR™ to amplify single-stranded mouse embryo cDNA prepared from normal CD-1 mouse embryo mRNA. A band of approximately 400 basepairs (bp) was isolated and purified by agarose gel electrophoresis, the DNA was ligated into the TA cloning vector (InVitrogen), and the ligation mixture was used to transform competent bacteria. Plasmid DNA (from 28 colony forming units) was prepared and evaluated by DNA sequence analysis. As determined by sequence identity comparison, 16/28 plasmid DNAs coded for mouse LTBP-1, 11/28 coded for mouse LTBP-3, and 1/28 coded for an apparently unique sequence. The insert DNA from the unique plasmid was then used as a probe to screen a cDNA library prepared from 3T3 cells (Stratagene, Inc.). A walking strategy eventually yielded the overlapping cDNA clones shown in FIG. [11] 7. Analysis of these clones identified an open reading frame of 5,430 base pairs. Comparison of sequence identity using the GAP and BESTFIT programs (Genetics Computer Group) revealed 79.7% identity between the mouse open reading frame and human LTBP-2 (Centrella *et al.*, 1991), but $\leq$ 47.1% identity between the mouse open reading frame and human LTBP-1 and mouse LTBP-3. The sequence comparison data agreed with chromosomal localization data, which collectively established that the sequence was the mouse homolog of human LTBP-2.

At page 78, lines 24-25 of the specification, the changes are as marked:

The complete cDNA nucleotide sequence for murine LTBP-2 is shown in [(SEQ ID NO:1) (FIG. 7)] SEQ ID NO:1. The deduced amino acid sequence is shown in [(SEQ ID NO:2) (FIG. 8)] SEQ ID NO:2.

At page 78, line 29 to page 79, line 27 of the specification, the changes are as marked:

The inventors have demonstrated that *ltbp-3* is widely and intensely expressed in both developing maternal tissues (*e.g.*, uterine decidua) and mouse embryo tissues (*e.g.*, mesenchyme, connective tissue, epithelia, and parenchyma). Tissue *in situ* hybridization was used to compare and contrast the developmental expression of *ltbp-2* and *ltbp-3*. [FIG. 12A, FIG. 12B, and FIG 12C] FIG. 8A, FIG. 8B and FIG. 8C present an overview of *ltbp-2* expression in a mid-sagittal section of a mouse embryo at day 16.5 *p.c.* of development, when expression is strongest. The section was hybridized with a ^{35}S-labeled single stranded antisense riboprobe synthesized from a

580 base pair cDNA coding for the mouse LTBP-2 3' untranslated region. The probe showed <30% sequence identity with the 3' untranslated sequences of human *ltbp-1* and *ltbp-2*, which is too low to give spurious hybridization signals under our conditions. A ^{35}S-labeled single stranded normal sense riboprobe from the same cDNA construct was used as a negative control. *ltbp-2* expression above background was observed in the snout, base of the skull, tail, paw, lung, vertebrae, and large vessels of mouse embryos. Microscopy of day 16.5 *p.c.* embryo tissue sections, taken from the same slide used to prepare whole mount sections shown in [FIG. 12A] FIG. 8A, demonstrated that the pattern of hybridization was due to significant *ltbp-2* gene expression by perichondrial and vascular wall cells. Positive signals were detected, for example, in perichondrial cells of cartilage aggregates located in the vertebral column (v), forelimb and tail, and at the base of the skull ([FIG. 12B] FIG. 8B). Indeed, the perichondrium (pc) of all cartilage aggregates observed in these mouse embryo tissue sections was positively hybridized. *ltbp-2* was also expressed by vascular wall cells of the aorta (ao), and in blood vessels within lung parenchyma and within the connective tissue supporting hair follicle structures associated with the snout (s). In contrast, *ltbp-2* was expressed at insignificant levels (*i.e.*, below the experimental background) in the generalized mesenchyme/connective tissue, brain, peripheral nerve, tooth rudiment, lung epithelium, cardiac and skeletal muscle, gut epithelium, liver parenchyma, pancreas epithelium and islets of Langerhans, brown fat cells, and kidney parenchyma. These *in situ* hybridization results, which were reproduced using independent tissue sections, demonstrate for the first time that *ltbp-2* expression in developing mouse tissues is more restricted than that of *ltbp-3*.